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CHEMICAL COMPOUNDS

The present invention concerns piperidine derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in WO99/38514, WO99/04794 and WO00/35877.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system. Chemokines play an important rôle in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

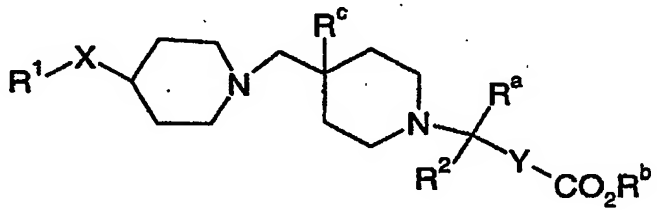
Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

Histamine is a basic amine, 2-(4-imidazolyl)-ethylamine, and is formed from histidine by histidine decarboxylase. It is found in most tissues of the body, but is present

in high concentrations in the lung, skin and in the gastrointestinal tract. At the cellular level inflammatory cells such as mast cells and basophils store large amounts of histamine. It is recognised that the degranulation of mast cells and basophils and the subsequent release of histamine is a fundamental mechanism responsible for the clinical manifestation of an allergic process. Histamine produces its actions by an effect on specific histamine G-protein coupled receptors, which are of three main types, H1, H2 and H3. Histamine H1 antagonists comprise the largest class of medications used in the treatment of patients with allergic disorders, especially rhinitis and urticaria. H1 antagonists are useful in controlling the allergic response by for example blocking the action of histamine on post-capillary venule smooth muscle, resulting in decreased vascular permeability, exudation and oedema. The antagonists also produce blockade of the actions of histamine on the H1 receptors on c-type nociceptive nerve fibres, resulting in decreased itching and sneezing.

Viral infections are known to cause lung inflammation. It has been shown experimentally that the common cold increases mucosal output of eotaxin in the airways. Instillation of eotaxin into the nose can mimic some of the signs and symptoms of a common cold. (See, Greiff L *et al* Allergy (1999) 54(11) 1204-8 [Experimental common cold increase mucosal output of eotaxin in atopic individuals] and Kawaguchi M *et al* Int. Arch. Allergy Immunol. (2000) 122 S1 44 [Expression of eotaxin by normal airway epithelial cells after virus A infection].)

The present invention provides a compound of formula (I):



(I)

wherein:

X is CH_2, C(O), O, S, S(O), $S(O)_2$ or NR^3;

Y is a bond, C_{1-6} alkylene (optionally substituted by C_{1-4} alkyl or phenyl) or phenylene (optionally substituted by halogen, hydroxy, C_{1-4} alkyl or C_{1-4} alkoxy);

R^a and R^b are, independently, hydrogen or C_{1-4} alkyl;

R^c is hydrogen or hydroxy;

R^1 is hydrogen, C_{1-6} alkyl, aryl or heterocyclyl;

R^2 is hydrogen, C_{1-6} alkyl, aryl or heterocyclyl;

wherein, unless stated otherwise, the foregoing aryl and heterocyclyl moieties are optionally substituted by: halogen, cyano, nitro, hydroxy, oxo, $S(O)_pR^4$, $OC(O)NR^5R^6$, NR^7R^8, $NR^9C(O)R^{10}$, $NR^{11}C(O)NR^{12}R^{13}$, $S(O)_2NR^{14}R^{15}$, $NR^{16}S(O)_2R^{17}$, $C(O)NR^{18}R^{19}$, $C(O)R^{20}$, CO_2R^{21}, $NR^{22}CO_2R^{23}$, C_{1-6} alkyl, CF_3, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkoxy, OCF_3, C_{1-6} alkoxy(C_{1-6})alkoxy, C_{1-6} alkylthio, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl (itself optionally substituted by C_{1-4} alkyl or oxo), methylenedioxy, difluoromethylenedioxy, phenyl, phenyl(C_{1-4})alkyl, phenoxy, phenylthio, phenyl(C_{1-4})alkoxy, heterocyclyl, heterocyclyl(C_{1-4})alkyl, heterocyclyloxy or heterocyclyl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heterocyclyl moieties are optionally substituted with halogen, hydroxy, nitro, $S(O)_q(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 below), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 below), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3;

p and q are, independently, 0, 1 or 2;

R^3, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-6}$ alkenyl), phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 below), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 below), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 below), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 below), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3);

alternatively NR^5R^6, NR^7R^8, $NR^{12}R^{13}$, $NR^{14}R^{15}$, $NR^{18}R^{19}$, may, independently, form a 4-7 membered heterocyclic ring, azetidine, pyrrolidine, piperidine, azepine, morpholine or piperazine, the latter optionally substituted by C_{1-4} alkyl on the distal nitrogen;

R^4, R^{17} and R^{23} are, independently, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-6}$ alkenyl), phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3);

or an N-oxide thereof; or a pharmaceutically acceptable salt thereof; or a solvate thereof.

Certain compounds of the present invention can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers all such isomers and mixtures thereof in all proportions.

Suitable salts include acid addition salts such as a hydrochloride, dihydrochloride, hydrobromide, phosphate, acetate, diacetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulfonate or *p*-toluenesulfonate. Another example of an addition salt is sulfate.

The compounds of the invention may exist as solvates (such as hydrates) and the present invention covers all such solvates.

Halogen includes fluorine, chlorine, bromine and iodine. Halogen is, for example, fluorine or chlorine.

Alkyl groups and moieties are straight or branched chain and comprise, for example, 1 to 6 (such as 1 to 4) carbon atoms. Examples of alkyl groups are methyl, ethyl, n-propyl, iso-propyl or tert-butyl.

Alkenyl groups comprise, for example, 2 to 6 (such as 2 to 4) carbon atoms. Examples of alkenyl groups are vinyl or allyl.

In one embobiment cycloalkyl groups comprise from 3 to 10 (such as 3 to 8, for example 3 to 6) carbon atoms and are mono-, bi or tricyclic. Cycloalkyl is, for example, cyclopropyl, cyclopentyl, cyclohexyl, norbornyl or camphoryl. The cycloalkyl ring is optionally fused to a benzene ring (for example forming a bicyclo[4.2.0]octa-1,3,5-trienyl or indanyl ring system).

In another embodiment cycloalkenyl comprises from 3 to 8 (such as from 3 to 6) carbon atoms and is, for example, monocyclic. Cycloalkenyl is, for example, cyclopentenyl or cyclohexenyl.

Aryl includes phenyl or naphthyl.

Heterocyclyl is an aromatic or non-aromatic 5 or 6 membered ring, optionally fused to one or more other rings, comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulfur; or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Heterocyclyl is, for example, furyl, thienyl (also known as thiophenyl), pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, piperidinyl, morpholinyl, pyridinyl, dihydropyridinyl (for example in a 6-oxo-1,6-dihydro-pyridinyl moiety), pyrimidinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl (also known as benzfuryl), benz[b]thienyl (also known as benzthienyl or benzthiophenyl), 2,3-dihydrobenz[b]thienyl (for example in a 1-dioxo-2,3-dihydrobenz[b]thienyl moiety), indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl (for example in a 1H-benzthiazol-2-one-yl moiety), 2,3-dihydrobenzthiazolyl (for example in a 2,3-dihydrobenzthiazol-2-one-yl moiety), 1,2,3-benzothiadiazolyl, an imidazopyridinyl (such as imidazo[1,2a]pyridinyl), thieno[3,2-b]pyridin-6-yl 1,2,3-benzoxadiazolyl (also known as benzo[1,2,3]thiadiazolyl), 2,1,3-benzothiadiazolyl, benzofurazan (also known as 2,1,3-benzoxadiazolyl), quinoxalinyl, dihydro-1-benzopyryliumyl (for example in a coumarinyl or a chromonyl moiety), 3,4-dihydro-1H-2,1-benzothiazinyl (for example in a 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl moiety), a pyrazolopyridine (for example 1H-pyrazolo[3,4-b]pyridinyl), a purine (for example in a 3,7-dihydro-purin-2,6-dione-8-yl moiety), quinolinyl, isoquinolinyl, dihydroisoquinolinyl (for example in a 2H-isoquinolin-1-one-yl moiety), a naphthyridinyl (for example [1,6]naphthyridinyl or [1,8]naphthyridinyl), a dihydro[1,8]naphthyridinyl (for example in a 1H-[1,8]naphthyridin-4-one-yl moiety), a benzothiazinyl, a dihydrobenzothiazinyl (for example in a 4H-benzo[1,4]thiazin-3-one-yl moiety), benzo[d]imidazo[2,1-b]thiazol-2-yl or dibenzothiophenyl (also known as dibenzothienyl); or an N-oxide thereof, or an S-oxide or S-dioxide thereof.

An N-oxide of a compound of formula (I) is, for example, a 1-oxy-[1,4']bipiperidinyl-1'-yl compound.

In one particular aspect the invention provides a compound of formula (I) wherein X is O.

In another aspect R^1 is phenyl optionally substituted (for example independently mono- or di-substituted) with halogen (for example chlorine or fluorine), C_{1-4} alkyl (for example methyl) or C_{1-4} alkoxy (for example methoxy).

In a further aspect R^1 is phenyl optionally substituted (for example with one, two or three of the same or different) with fluorine, chlorine, C_{1-4} alkyl (for example methyl) or C_{1-4} alkoxy (for example methoxy). In a still further aspect R^1 is phenyl substituted by one, two or three (for example two or three) substituents independently selected from: fluorine, chlorine and methyl. For example R^1 is 3,4-dichlorophenyl, 2,4-dichloro-3-methylphenyl, 3,4-dichloro-2-methylphenyl, 2,4-dichlorophenyl, 4-chloro-2-methylphenyl or 2-chloro-4-fluorophenyl.

In another aspect R^a is hydrogen.

In another aspect R^b is hydrogen or methyl.

In another aspect R^c is hydrogen.

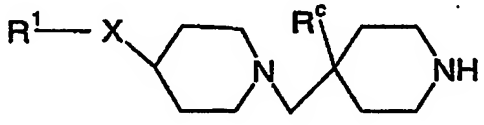
In a further aspect R^2 is unsubstituted phenyl or naphthyl, mono-, di- or tri-substituted phenyl or naphthyl or mono-substituted heterocyclyl, the substituents being chosen from those described above.

Heterocyclyl is, for example, pyrimidinyl or pyridinyl. In a further aspect of the invention heterocyclyl is optionally substituted by C_{1-4} alkyl or C_{1-4} alkoxy.

In another aspect R^2 is hydrogen or phenyl optionally substituted by: halogen (for example fluoro), C_{1-6} alkyl, C_{1-6} alkoxy or (C_{1-6} alkyl)C(O)NH.

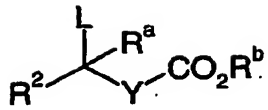
In a further aspect the present invention provides a compound of formula (I) wherein X is O; R^1 is phenyl optionally substituted by halogen (for example chlorine) or C_{1-4} alkyl (for example methyl); and R^a, R^b, R^c and R^2 is as defined above.

A compound of formula (I), preferably wherein R^a is hydrogen, can be prepared by coupling a compound of formula (II):



(II)

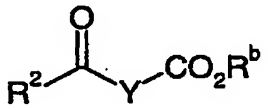
with a compound of formula (III):



(III)

wherein L is a suitable leaving group (such as halogen (such as chloro or bromo), C_{1-6} alkylsulfonyl (such as mesylate) or tosylate) and the coupling can be carried out in a suitable solvent (such as water or N,N-dimethylformamide) at ambient temperature.

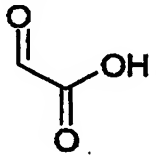
Alternatively, a compound of formula (I), wherein R^a is hydrogen, can be prepared by reductive amination of a compound (II) with a compound of formula (IV):



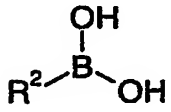
(IV)

wherein R^b is C_{1-4} alkyl, in the presence of $NaBH(OAc)_3$ and acetic acid, or $NaBH_3CN$ in a suitable solvent (such as tetrahydrofuran), optionally followed by hydrolysis of the ester group.

Alternatively, a compound of formula (I), wherein Y is a bond and R^a and R^b are both hydrogen, can be prepared by a three component coupling of a compound of formula (II) with compounds of formula (V) and (VI):



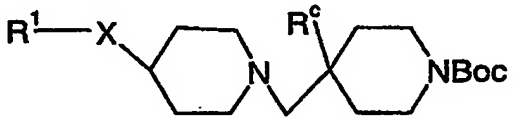
(V)



(VI)

in a suitable solvent (such as a C_{1-6} aliphatic alcohol (for example ethanol)) at a suitable elevated temperature (for example reflux; such as 60-100°C).

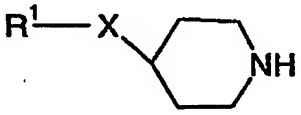
A compound of formula (II) can be prepared by deprotecting a compound of formula (VII):



(VII)

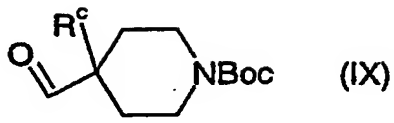
for example using trifluoroacetic acid in a suitable solvent (such as dichloromethane) or using a source of hydrogen chloride in a suitable solvent (such as dioxane).

A compound of formula (VII), wherein R^c is hydrogen, can be prepared by reacting a compound of formula (VIII):



(VIII)

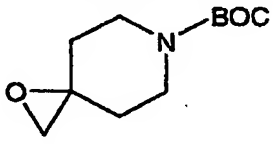
with a compound of formula (IX):



(IX)

in the presence of $NaBH(OAc)_3$ and acetic acid, in a suitable solvent (such as tetrahydrofuran or dichloromethane).

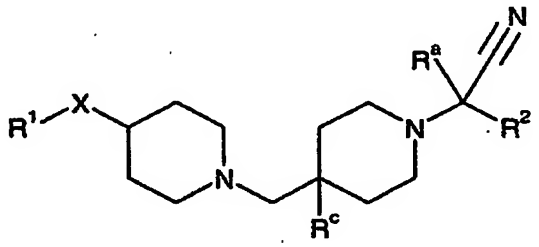
A compound of formula (VII), wherein R^c is hydroxy, can be prepared by reacting a compound of formula (VIII) with a compound of formula (X):



(X)

in a suitable solvent (such as a C_{1-6} aliphatic alcohol, for example ethanol) at room temperature.

A compound of formula (I), wherein Y is a bond and R^b is hydrogen, can be prepared by performing a nitrile hydrolysis on a compound of formula (XI):



(XI)

Such a hydrolysis can be carried out by refluxing a mixture of hydrochloric acid and ethanol; or by adding $MeSO_3H$, water and hydrochloric acid and then refluxing the mixture.

A compound of formula (XI) can be prepared by reacting a compound of formula (II) with $R^aR^2C(O)$ and titanium isopropoxide ($Ti(OiPr)_4$), followed by Et_2AlCN.

The preparation of various intermediates can be found in WO00/66559 and WO01/77101; alternatively they can be prepared by using or adapting literature methods.

Further compounds of formula (I) can be prepared by adaptation of: the routes described above, methods described in the art or the Examples recited below.

Compounds of formula (III) to (IX) can be prepared by using or adapting methods described in the art. The preparation of various phenoxy piperidines is described in WO 01/77101.

A compound of formula (I), wherein Y is CHR^d and R^d is hydrogen, C_{1-4} alkyl or phenyl, can be prepared by reacting a compound of formula (II) with an alkene of formula $R^2R^aC{=}CHR^dCO_2R^b$ in a suitable solvent, such as ethanol, at a suitable elevated temperature, such as 50-100°C.

A compound of formula (I), wherein R^a is hydrogen and Y is CH_2, can be prepared by reacting a compound of formula (II) with an alkyne of formula $R^2C{\equiv}CCO_2R^b$ in a suitable solvent, such as ethanol, at a suitable elevated temperature, such as 50-100°C; and then reducing the alkene product so formed (for example by catalytic hydrogenation).

A compound of formula (I), wherein R^2 and R^a are hydrogen and Y is phenylene (optionally substituted by halogen, hydroxy, C_{1-4} alkyl or C_{1-4} alkoxy), can be prepared by reacting a compound of formula (II) with a benzyl bromide of formula $BrCH_2$-Y-CO_2R^b in the presence of diisopropylethylamine (DIPEA), in a suitable solvent (such as acetonitrile) and at ambient temperature (such as in the range 10-30°C).

Alternatively, a compound of formula (I), wherein R^2 and R^a are hydrogen and Y is phenylene (optionally substituted by halogen, hydroxy, C_{1-4} alkyl or C_{1-4} alkoxy), can be prepared by reacting a compound of formula (II) with a benzaldehyde of formula (O)HC-Y-CO_2R^b wherein R^b is C_{1-4} alkyl, in the presence of $NaBH(OAc)_3$ and acetic acid, in a suitable solvent (such as tetrahydrofuran), optionally followed by hydrolysis of the ester group.

In another aspect the present invention provides processes for the preparation of compounds of formula (I).

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially CCR3) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).

Examples of these conditions are:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis

medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, lichen planus, phemphigus, bullous phemphigus, epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, alopecia areata, corneal ulcer or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), peridontal disease, Sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle.

The compounds of formula (I) or a pharmaceutically acceptable salt thereof or a solvate thereof, are also H1 antagonists (and can, therefore, be used in the treatment of allergic disorders); and may also be used to control a sign and/or symptom of what is commonly referred to as a cold (for example a sign and/or symptom of a common cold or influenza or other associated respiratory virus infection).

According to a further feature of the present invention there is provided a method for treating a chemokine mediated disease state (especially a CCR3 mediated disease state)

in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof or a solvate thereof.

According to another feature of the present invention there is provided a method for antagonising H1 in a mammal, such as man, suffering from, or at risk of, an H1 mediated disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof or a solvate thereof.

According to yet another feature of the present invention there is provided a method for treating a sign and/or symptom of what is commonly referred to as a cold in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof or a solvate thereof.

The invention also provides a compound of the formula (I), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use in therapy.

In another aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR3 receptor activity), antagonising H1 or treating a sign and/or symptom of what is commonly referred to as a cold).

The invention further provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis

nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behcet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, lichen planus, phemphigus, bullous phemphigus, epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, alopecia areata, corneal ulcer or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle;

in a mammal (for example man).

In a further aspect the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In a still further aspect a compound of formula (I), or a pharmaceutically acceptable salt thereof, is useful in the treatment of asthma.

The present invention also provides a the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof, for the therapeutic treatment of a mammal, such as man, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof or a solvate thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier.

In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art. A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

Each patient may receive, for example, a dose of $0.01mgkg^{-1}$ to $100mgkg^{-1}$, preferably in the range of $0.1mgkg^{-1}$ to $20mgkg^{-1}$, of the active ingredient administered, for example, 1 to 4 times per day.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) when given, ^1H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300MHz or 400MHz using perdeuterio DMSO-D6 (CD_3SOCD_3) or $CDCl_3$ as the solvent unless otherwise stated;

(ii) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI) or fast atom bombardment (FAB); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(iii) the title and sub-title compounds of the examples and methods were named using the index name program from Advanced Chemistry Development Inc;

(iv) unless stated otherwise, reverse phase HPLC was conducted using a Symmetry™, NovaPak™ or Xerra™ reverse phase silica column; and

(v) the following abbreviations are used:

Boc or BOC	tert-butoxycarbonyl
HPLC	high pressure liquid chromatography
DIPEA	Diisopropylethylamine

DMSO	dimethylsulfoxide
aq	aqueous

INTERMEDIATE 1

4-(3,4-dichlorophenoxy)-1-(4-piperidinylmethyl)-piperidine

a) 1,1-Dimethylethyl 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidinecarboxylate

4-(3,4-Dichlorophenoxy)piperidine (1.27g) was dissolved in tetrahydrofuran (20ml); acetic acid (0.5ml) and 1,1-dimethylethyl 4-formyl-1-piperidinecarboxylate (1.43g) were added to the solution. The reaction mixture was stirred at room temperature for 30min then sodium triacetoxyborohydride (1.53g) was added and the mixture was stirred at room temperature overnight. The reaction mixture was poured into 2M sodium

hydroxide solution (50ml) and product was extracted with ether. The ether was washed with brine, dried, filtered and evaporated. Crude material was purified by flash chromatography (eluting with 979 : 20 :1 dichloromethane : methanol : aqueous ammonia) to give the subtitle compound (2.15g).

MS 443/445 $[M+H]^+$ (ES+)

^{1}H NMR δ ($CDCl_3$) 1.06 (2H, ddd), 1.45 (9H, s), 1.61 - 1.82 (5H, m), 1.92 - 1.98 (2H, m), 2.16 - 2.27 (4H, m), 2.65 - 2.73 (4H, m), 4.08 (2H, d), 4.25 (1H, dq), 6.75 (1H, dd), 6.99 (1H, d), 7.30 (1H, d)

b) 4-(3,4-dichlorophenoxy)-1-(4-piperidinylmethyl)-piperidine

1,1-Dimethylethyl 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidinecarboxylate (1.0g) was added to a mixture of 20% TFA in dichloromethane (20ml) and the mixture was stirred at room temperature for 1h. Solvent was removed by evaporation and 2M sodium hydroxide solution (25ml) was added to the residue. Product was extracted with ethyl acetate. The organic phase was washed with brine, dried, filtered and evaporated to give the title compound (0.5g).

MS 343/345 $[M+H]^+$ (ES+)

^{1}H NMR δ ($CDCl_3$) 1.10 (2H, qd), 1.60 (1H, qquintet), 1.73 - 1.83 (4H, m), 1.90 - 2.01 (2H, m), 2.16 - 2.26 (4H, m), 2.55 - 2.70 (4H, m), 3.09 (2H, d), 4.24 (1H, dquintet), 6.75 (1H, dd), 6.99 (1H, d), 7.27 (1H, d)

The following intermediates were prepared analogously from the appropriate aryloxy piperidine:

Intermediate	Name	M+H	^{1}H NMR
2	4-(2,4-dichloro-3-methylphenoxy)-1-(4-piperidinylmethyl)-piperidine	357/359	δ ($CDCl_3$) 1.13 - 1.27 (2H, m), 1.57 - 1.70 (1H, m), 1.76 - 2.00 (2H, m), 2.16 - 2.32 (4H, m), 2.46 (3H, s), 2.60 - 2.99 (8H, m), 3.16 (2H, d), 4.31 (1H, quintet), 6.75 (1H, d), 7.18 (1H, d)

3	4-(4-chloro-2-methylphenoxy)-1-(4-piperidinylmethyl)-piperidine	322/324	δ ($CDCl_3$) 1.08 - 1.21 (2H, m), 1.56 - 1.68 (1H, m), 1.73 - 1.86 (4H, m), 1.90 - 1.99 (2H, m), 2.16 - 2.31 (7H, m), 2.57 - 2.69 (4H, m), 3.12 (2H, d), 4.23 - 4.31 (1H, m), 6.74 (1H, d), 7.06 (1H, dd), 7.11 (1H, d)

INTERMEDIATE 4

4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]- 4-piperidinol

a) 1,1-Dimethylethyl 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-4-hydroxy-1-piperidinecarboxylate

A solution of 4-(3,4-dichlorophenoxy)-piperidine (5.2g) and 1,1-dimethylethyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (4.1g) in ethanol (50ml) was stirred at room temperature for 18 hours and then at 60°C for 18 hours. The solvent was evaporated to leave 9.5g of a pale yellow oil. Flash chromatography (dichloromethane then dichloromethane : 7M ammonia in methanol 95:5) gave the subtitle compound (8.48g).

MS $[M+H]^+$ (ES+) 459/461

^1H NMR δ ($CDCl_3$) 1.35 - 1.63 (4H, m), 1.46 (9H, s), 1.73 - 1.86 (2H, m), 1.89 - 2.01 (2H, m), 2.34 (2H, s), 2.49 - 2.59 (2H, m), 2.79 - 2.89 (2H, m), 3.07 - 3.24 (2H, m), 3.79 - 3.93 (2H, m), 4.22 - 4.32 (1H, m), 6.75 (1H, dd), 6.99 (1H, d), 7.30 (1H, d)

b) 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-4-piperidinol

To a solution of 1,1-dimethylethyl 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-4-hydroxy-1-piperidinecarboxylate (5g) in dichloromethane (50ml) was added trifluoroacetic acid (5ml) and the solution was stirred for 12 hours. Sodium hydroxide solution (1M) was added to give an alkaline solution, this was then extracted thrice with dichloromethane. The pooled organic phase was subsequently washed with water, dried, filtered and evaporated to give the title compound (3.5g).

MS $[M+H]^+$ (ES+) 359/361

^1H NMR δ ($CDCl_3$) 1.57 - 1.66 (4H, m), 1.69 - 1.84 (2H, m), 1.93 - 2.04 (2H, m), 2.36 (2H, s), 2.47 - 2.58 (2H, m), 2.82 - 2.92 (4H, m), 2.96 - 3.07 (2H, m), 4.32 - 4.41 (1H, m), 6.89 (1H, dd), 7.09 (1H, d), 7.38 (1H, d)

EXAMPLE 1

This Example illustrates the preparation of 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-α-phenyl-1-piperidineacetic acid.

4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidine (0.5g), and benzene boronic acid (0.2g) were dissolved in ethanol (3ml); glyoxylic acid (0.2ml of a 50% solution in water) was added to the solution and the reaction mixture was heated in a microwave oven at 100°C for 5min. The resultant solution was purified by RPHPLC (gradient 95% - 5% aqueous ammonium acetate, 5% - 95% acetonitrile) to give the title compound (0.1 g).

MS $[M+H]^+$ (ES+) 477/479

^{1}H NMR δ ($CDCl_3$) 1.53 - 1.77 (4H, m), 1.79 - 1.94 (4H, m), 2.14 - 2.25 (4H, m), 2.41 (1H, t), 2.54 - 2.64 (2H, m), 2.75 (1H, t), 3.38 (1H, d), 3.58 - 3.70 (2H, m), 4.15 - 4.23 (1H, m), 4.47 (1H, s), 6.71 (1H, dd), 6.96 (1H, d), 7.25 (1H, d), 7.32 - 7.38 (3H, m), 7.49 - 7.58 (2H, m).

Examples 2-18 (see Table I below) were made using the method of Example 1.

EXAMPLE 19

This Example illustrates the preparation of methyl 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-α-phenyl-piperidineacetate.

4-(3,4-Dichlorophenoxy)-1-(4-piperidinylmethyl)-piperidine (0.30g) and methyl-α-bromobenzeneacetate (0.22g) were dissolved in acetone (20mL) and potassium carbonate (0.13g) was added. The reaction mixture was stirred at room temperature for 16 h. The suspension was filtered and the filtrate was evaporated. The residue was chromatographed eluting with ethyl acetate : methanol : triethylamine (20 : 1 : 0.001) to give the title compound (0.24g).

MS $[M+H]^+$ (ES+) 491/493

^{1}H NMR δ (CD_3OD) 1.22 (1H, qd), 1.34 (2H, qd), 1.50 - 1.59 (1H, m), 1.66 (1H, d), 1.70 - 1.80 (3H, m), 1.88 (1H, td), 1.93 - 2.02 (2H, m), 2.14 (1H, td), 2.22 (2H, d), 2.25 - 2.33 (1H, m), 2.65 - 2.73 (3H, m), 2.95 - 3.01 (1H, m), 3.68 (3H, s), 3.98 (1H, s), 4.37 (1H, septet), 6.87 (1H, dd), 7.08 (1H, d), 7.31 - 7.38 (4H, m), 7.42 (2H, dd)

EXAMPLES 20 & 21

This Example illustrates the preparation of (R)-methyl 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-α-phenyl-piperidineacetate and (S)-methyl 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-α-phenyl-piperidineacetate.

Racemic methyl 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-α-phenyl-piperidineacetate (360mg) was dissolved in isohexane : isopropanol (9:1) and was chromatographed on a Chiralpack AD column eluting isohexane : isopropanol (9:1) to give the 2 isomers.

First eluting isomer (50mg); MS $[M+H]^+$ (ES+) 491/493. Retention time (chiralpack AD column (4.6 x 250mm), maintained at 10°C, flow rate 1mL/min 95:5 isohxane : isopropanol containing 0.1% diethylamine) 7.2 minutes.

Second eluting isomer (30mg); MS $[M+H]^+$ (ES+) 491/493. Retention time (chiralpack AD column (4.6 x 250mm), maintained at 10°C, flow rate 1mL/min 95:5 isohxane : isopropanol containing 0.1% diethylamine) 8.9 minutes.

EXAMPLE 22

This Example illustrates the preparation of methyl 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidineacetate

To a stirred solution of 4-(3,4-dichlorophenoxy)-1-(4-piperidinylmethyl)-piperidine (0.23 g) and DIPEA (0.164 mL) in DMF at RT was added methyl bromoacetate (0.076 mL). The reaction was heated at 60 °C for 16 h. Saturated sodium bicarbonate solution (30 mL) was then added to the cooled solution and the product was extracted into ethyl acetate (3 x 20 mL). The combined organics were washed with brine (10 mL) and then dried, filtered and evaporated to leave a colourless oil (0.135 g).

MS $[M+H]^+$ (ES+) 415/417

Examples 23 and 24 (see Table I) were prepared analogously to Example 22 from the appropriate amine.

EXAMPLE 25

This Example illustrates the preparation of methyl (2*R*)-2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)propanoate

Diethyl ether (10ml) and dimethylformamide (2ml) were added to 4-(3,4-dichlorophenoxy)-1-(piperidin-4-ylmethyl)piperidine (0.32g) and the mixture was sonicated (cleaning bath) until it became clear. Methyl (2*S*)-2-bromopropanoate (0.16g) and triethylamine (0.6ml) were added and the mixture was stirred at room temperature overnight. The reaction mixture was poured into water and was extracted with diethyl ether. The diethyl ether was washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an oil. Crude product was purified by chromatography, eluting with 95 : 5 : 0.1 dichloromethane : methanol : aqueous ammonia to give the title compound as an oil (0.25g).

MS $[M+H]^+$ (ES+) 429/431

Example 26 (see Table I) was prepared analogously to Example 25.

EXAMPLE 27

This Example illustrates the preparation of 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidineacetic acid.

Methyl 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidineacetate (0.135 g) and lithium hydroxide (0.136 g) in 3 :1 methanol/water (2ml) was stirred at RT for 16 h. The reaction mixture was acidified to pH 4 with acetic acid and purified by RPHPLC (10% MeCN/90%NH_4OAc aq (0.1%) gradient to 70% MeCN/30%NH_4OAc) to provide the title compound as a white solid (0.030g).

MS $[M+H]^+$ (ES+) 401/403.

^1H NMR δ (CD_3OD) 1.52 (2H, qd), 1.72 - 1.92 (3H, m), 1.98 - 2.09 (4H, m), 2.34 (2H, d), 2.38 - 2.45 (2H, m), 2.72 - 2.83 (2H, m), 3.01 (2H, td), 3.56 - 3.67 (4H, m), 4.35 - 4.49 (1H, m), 6.90 (1H, dd), 7.11 (1H, d), 7.39 (1H, d).

Examples 28-31 and 36 (see Table I) were prepared analogously to Example 27 from the appropriate ester.

EXAMPLE 32

This Example illustrates the preparation of 4-[[4-(3,4-Dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidine propanoic acid

To a stirred solution of 4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidine (0.175 g) in isopropanol (0.4 mL) at RT was added acrylic acid (0.038 mL). After 16 h the reaction mixture was purified by HPLC (5% MeCN/95%NH_4OAc aq (0.1%) gradient to 50% MeCN/50%NH_4OAc). Treatment of the product with 2 M HCl at 40 °C for 15 min followed by evaporation left a yellow solid. This was triturated with diethyl ether (3 mL) and the residual solid was partially dissolved in 4 : 1 dichloromethane/methanol. The supernatant was evaporated to provide the title compound as a solid (0.014g).

MS $[M+H]^+$ (ES+) 415/417.

^1H NMR $\delta(D_2O)$ 1.63 (2H, qd), 1.91 - 2.05 (1H, m), 2.09 - 2.21 (2H, m), 2.26 (2H, d), 2.29 - 2.36 (1H, m), 2.40 (1H, d), 2.87 (2H, t), 3.08 (2H, t), 3.14 - 3.22 (2H, m), 3.29 - 3.40 (2H, m), 3.44 (2H, t), 3.52 (1H, d), 3.64 - 3.79 (3H, m), 4.61 - 4.70 (1H, m), 6.96 - 7.03 (1H, m), 7.24 - 7.29 (1H, m), 7.50 (1H, d).

EXAMPLE 33

This Example illustrates the preparation of methyl 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-α,α-dimethyl-1-piperidine propanoate

To a stirred solution of 4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidine (0.175 g) and 2,2-dimethyl-3-oxopropanoic acid methyl ester (80 mg) in tetrahydrofuran (0.5 mL) was added sodium triacetoxyborohydride (162 mg) and acetic acid (0.041 mL). The reaction mixture was stirred at room temperature overnight. Saturated sodium bicarbonate solution (30 mL) was added and the product was extracted into ethyl acetate (3 x 20 mL). The combined organics were washed with brine (10 mL) and dried ($MgSO_4$), filtered and evaporated to leave an oil (0.17 g). A portion (0.080 g) was purified by HPLC (5% MeCN/95%NH_4OAc aq (0.1%) gradient to 5% MeCN/95%NH_4OAc) to give the title compound as an oil (0.012 g).

MS $[M+H]^+$ (ES+) 457/459.

^1H NMR $\delta(CDCl_3)$ 1.15 (6H, s), 1.16 (1H, qd), 1.34 - 1.45 (1H, m), 1.58 - 1.62 (2H, m), 1.62 - 1.66 (2H, m), 1.71 - 1.82 (2H, m), 1.90 - 2.00 (2H, m), 2.07 - 2.16 (3H, m), 2.16 - 2.26 (2H, m), 2.45 (2H, s), 2.60 - 2.70 (2H, m), 2.70 - 2.77 (2H, m), 3.65 (3H, s), 4.18 - 4.27 (1H, m), 6.74 (1H, dd), 6.99 (1H, d), 7.30 (1H, d).

EXAMPLE 34

This Example illustrates the preparation of 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-α,α-dimethyl-1-piperidine propanoic acid.

To a stirred solution of methyl 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-α,α-dimethyl-1-piperidine propanoate (0.080 g) in THF (1 mL) at RT was added potassium trimethylsilanolate (27 mg). After 16 h the reaction mixture was incomplete and further potassium trimethylsilanolate (27 mg) was added. After a further 1 h the reaction solvent was evaporated and the residue was redissolved in acetonitrile and purified by HPLC (5% MeCN/95%NH_4OAc aq (0.1%) gradient to 60% MeCN/40%NH_4OAc) to give the title compound (0.036g).

MS $[M+H]^+$ (ES+) 443/445.

^1H NMR δ(CD_3OD) 1.22 (6H, s), 1.47 (2H, q), 1.68 - 1.81 (2H, m), 1.79 - 1.88 (1H, m), 1.93 - 2.05 (4H, m), 2.27 (2H, d), 2.33 (2H, t), 2.67 - 2.76 (2H, m), 2.95 - 3.02 (2H, m), 3.04 (2H, s), 3.45 - 3.52 (2H, m), 4.33 - 4.42 (1H, m), 6.87 (1H, dd), 7.08 (1H, d), 7.36 (1H, d).

EXAMPLE 35

This Example illustrates the preparation of methyl 2-[(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)methyl]benzoate

4-(3,4-Dichlorophenoxy)-1-(piperidin-4-ylmethyl)piperidine (0.5g) was dissolved in acetonitrile (2ml) and to the solution was added methyl 2-(bromomethyl)benzoate (0.56g) and DIPEA (0.25ml). The reaction mixture was stirred at room temperature overnight then concentrated by evaporation under reduced pressure. The residue was partitioned between ethyl acetate and water, the organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated to give an oil. This was purified by chromatography eluting with 5% methanol in dichloromethane then by HPLC (25% MeCN/75%NH_4OAc aq (0.1%) gradient to 95% MeCN/5%NH_4OAc) to give the title compound as an oil 0.4g.

MS $[M+H]^+$ (ES+) 491/493.

^1H NMR δ ($CDCl_3$) 1.10 - 1.24 (2H, m), 1.46 (1H, qd), 1.63 - 2.05 (8H, m), 2.15 - 2.28 (4H, m), 2.62 - 2.71 (2H, m), 2.76 - 2.82 (2H, m), 3.74 (2H, s), 3.87 (3H, s), 4.23 (1H, quintet), 6.74 (1H, dd), 6.99 (1H, d), 7.25 - 7.32 (2H, m), 7.37 - 7.46 (2H, m), 7.68 (1H, d).

TABLE I

Example	Name	M+H	^{1}H NMR
2	4-[[4-(2,4-dichloro-3-methylphenoxy)-1-piperidinyl]methyl]-α-phenyl-1-piperidineacetic acid	491/493	δ ($CDCl_3$) 1.56 - 1.72 (3H, m), 1.83 - 1.97 (6H, m), 2.23 (2H, d), 2.30 - 2.39 (2H, m), 2.45 (3H, s), 2.50 - 2.52 (1H, m), 2.62 - 2.68 (2H, m), 2.76 - 2.84 (1H, m), 3.39 (1H, d), 3.71 (2H, d), 4.32 (1H, s), 4.57 (1H, s), 6.71 (1H, d), 7.17 (1H, d), 7.36 - 7.38 (3H, m), 7.53 - 7.56 (2H, m)
3	4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-α-(4-fluorophenyl)-1-piperidineacetic acid	495/497	δ ($CDCl_3$) 1.56 - 1.78 (5H, m), 1.84 - 1.98 (4H, m), 2.18 - 2.32 (4H, m), 2.37 - 2.53 (1H, m), 2.57 - 2.67 (2H, m), 2.72 - 2.84 (1H, m), 3.36 - 3.43 (1H, m), 3.64 - 3.72 (1H, m), 4.19 - 4.26 (1H, m), 4.54 (1H, s), 6.72 (1H, dd), 6.96 (1H, d), 7.07 (2H, t), 7.24 - 7.32 (1H, m), 7.55 (2H, dd)
4	4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-α-(2-methoxyphenyl)-1-piperidineacetic acid	507/509	δ ($CDCl_3$) 1.55 - 1.79 (5H, m), 1.86 - 2.00 (4H, m), 2.16 - 2.27 (4H, m), 2.39 - 2.74 (4H, m), 2.87 (1H, t), 3.37 (1H, d), 3.69 - 3.78 (1H, m), 3.87 (3H, s), 4.18 - 4.26 (1H, m), 5.03 (1H, s), 6.72 (1H, dd), 6.91 - 7.03 (3H, m), 7.25 - 7.31 (1H, m), 7.37 (1H, t), 7.51 (1H, d)
5	4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-α-(2-methylphenyl)-1-piperidineacetic acid	491/493	δ ($CDCl_3$) 1.47 - 1.75 (4H, m), 1.80 - 1.95 (5H, m), 2.12 - 2.23 (4H, m), 2.43 - 2.66 (6H, m), 2.76 - 2.90 (1H, m), 3.39 (1H, d), 3.49 (1H, s), 3.84 - 3.96 (1H, m), 4.14 - 4.25 (1H, m), 4.76 (1H, s), 6.72 (1H, dd), 6.96 (1H, d), 7.16 - 7.32 (4H, m), 7.78 (1H, d)

6	4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-α-(4-methylphenyl)-1-piperidineacetic acid	491/493	δ ($CDCl_3$) 1.55 - 1.79 (5H, m), 1.81 - 1.96 (4H, m), 2.14 - 2.25 (4H, m), 2.35 (3H, s), 2.43 - 2.73 (4H, m), 2.76 - 2.87 (1H, m), 3.47 (1H, d), 3.68 - 3.77 (1H, m), 4.15 - 4.25 (1H, m), 4.54 (1H, s), 6.72 (1H, dd), 6.96 (1H, d), 7.18 (2H, d), 7.26 - 7.31 (1H, m), 7.42 (2H, d)
7	4-[[4-(2,4-dichloro-3-methylphenoxy)-1-piperidinyl]methyl]-α-(2-methoxyphenyl)-1-piperidineacetic acid	521/523	δ ($CDCl_3$) 1.55 - 1.68 (2H, m), 1.74 - 2.00 (5H, m), 2.16 - 2.28 (4H, m), 2.45 (3H, s), 2.57 - 2.90 (6H, m), 3.41 (1H, d), 3.66 - 3.77 (1H, m), 3.87 (3H, s), 4.24 - 4.35 (1H, m), 5.09 (1H, s), 6.72 (1H, d), 6.92 - 7.02 (2H, m), 7.17 (1H, d), 7.36 (1H, dd), 7.53 (1H, d)
8	4-[[4-(2,4-dichloro-3-methylphenoxy)-1-piperidinyl]methyl]-α-(2-methylphenyl)-1-piperidineacetic acid	505/507	δ ($CDCl_3$) 1.73 - 1.96 (8H, m), 2.14 - 2.28 (5H, m), 2.45 (3H, s), 2.53 (3H, s), 2.57 - 2.66 (4H, m), 2.75 - 2.86 (1H, m), 3.36 (1H, d), 3.80 - 3.91 (1H, m), 4.24 - 4.32 (1H, m), 4.73 (1H, s), 6.71 (1H, d), 7.14 - 7.24 (4H, m), 7.77 (1H, d)
9	4-[[4-(2,4-dichloro-3-methylphenoxy)-1-piperidinyl]methyl]-α-(4-methylphenyl)-1-piperidineacetic acid	505/507	δ ($CDCl_3$) 1.55 - 1.94 (9H, m), 2.14 - 2.27 (4H, m), 2.35 (3H, s), 2.45 (3H, s), 2.52 - 2.82 (5H, m), 3.46 (1H, d), 3.64 - 3.73 (1H, m), 4.24 - 4.32 (1H, m), 4.47 (1H, s), 6.71 (1H, d), 7.17 (3H, d), 7.43 (2H, d)

10	4-[[4-(4-chloro-2-methylphenoxy)-1-piperidinyl]methyl]-α-(2-methoxyphenyl)-1-piperidineacetic acid	487/489	δ ($CDCl_3$) 1.58 - 1.65 (2H, m), 1.70 - 1.80 (4H, m), 1.85 - 1.95 (4H, m), 2.15 - 2.26 (7H, m), 2.46 - 2.74 (3H, m), 2.80 - 2.91 (1H, m), 3.42 (1H, d), 3.68 - 3.77 (1H, m), 3.87 (3H, s), 4.19 - 4.28 (1H, m), 5.09 (1H, s), 6.70 (1H, d), 6.91 - 7.11 (4H, m), 7.36 (1H, dd), 7.53 (1H, d)
11	4-[[4-(4-chloro-2-methylphenoxy)-1-piperidinyl]methyl]-α-(2-methylphenyl)-1-piperidineacetic acid	471/473	δ ($CDCl_3$) 1.48 - 1.95 (11H, m), 2.13 (3H, s), 2.25 (2H, t), 2.46 - 2.90 (8H, m), 3.36 (1H, d), 3.83 - 3.93 (1H, m), 4.19 - 4.28 (1H, m), 4.78 (1H, s), 6.70 (1H, d), 7.02 - 7.11 (2H, m), 7.15 - 7.25 (3H, m), 7.74 (1H, d)
12	α-[4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidinyl]-2,4-dimethoxy-5-pyrimidineacetic acid	539/541	δ ($CDCl_3$) 1.48 - 2.80 (19H, m), 3.27 - 3.35 (1H, m), 3.51 (3H, s), 3.99 (3H, s), 4.29 - 4.37 (1H, m), 4.55 (1H, s), 6.73 (1H, dd), 6.98 (1H, d), 7.31 (1H, d), 8.06 (1H, s)
13	4-[[4-(4-chloro-2-methylphenoxy)-1-piperidinyl]methyl]-α-(4-methylphenyl)-1-piperidineacetic acid	471/473	δ ($CDCl_3$) 1.56 - 1.79 (5H, m), 1.83 - 1.94 (4H, m), 2.13 - 2.27 (7H, m), 2.35 (3H, s), 2.44 - 2.95 (5H, m), 3.48 (1H, d), 3.71 (1H, d), 4.19 - 4.28 (1H, m), 4.50 (1H, s), 6.70 (1H, d), 7.03 - 7.11 (2H, m), 7.18 (2H, d), 7.43 (2H, d)

14	α-[3-(acetylamino)phenyl]-4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidineacetic acid	534/536	δ ($CDCl_3$) 1.46 - 1.64 (2H, m), 1.68 - 1.83 (3H, m), 1.87 - 1.97 (2H, m), 2.05 - 2.25 (7H, m), 2.36 - 2.77 (8H, m), 3.33 - 3.68 (2H, m), 4.22 (1H, s), 4.41 (1H, s), 6.73 (1H, dd), 6.96 - 7.02 (2H, m), 7.22 - 7.33 (2H, m), 7.49 (1H, s), 8.09 (1H, d)
15	4-[[4-(2,4-dichloro-3-methylphenoxy)-1-piperidinyl]methyl]-α-(4-fluorophenyl)-1-piperidineacetic acid	509/511	δ ($CDCl_3$) 1.54 - 2.47 (18H, m), 2.61 - 2.72 (2H, m), 3.28 - 3.35 (1H, m), 3.54 - 3.61 (1H, m), 4.29 - 4.42 (2H, m), 6.71 (1H, d), 7.05 (2H, t), 7.17 (1H, d), 7.54 (2H, dd)
16	4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-4-hydroxy-α-phenyl-1-piperidineacetic acid	493/495	δ (CD_3OD) 1.64 - 1.82 (4H, m), 1.85 - 2.03 (3H, m), 2.40 (2H, s), 2.49 - 2.57 (2H, m), 2.81 - 2.90 (3H, m), 2.98 - 3.16 (2H, m), 3.51 - 3.72 (2H, m), 4.32 - 4.39 (1H, m), 4.52 (1H, s), 6.87 (1H, dd), 7.08 (1H, d), 7.37 (1H, d), 7.42 - 7.47 (3H, m), 7.55 - 7.60 (2H, m)
17	4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-4-hydroxy-α-(4-methylphenyl)-1-piperidineacetic acid	507/509	δ (CD_3OD) 1.64 - 1.81 (4H, m), 1.82 - 2.02 (4H, m), 2.36 (3H, s), 2.40 (2H, s), 2.49 - 2.57 (2H, m), 2.81 - 2.89 (2H, m), 2.92 - 3.06 (2H, m), 3.62 - 3.75 (2H, m), 4.32 - 4.39 (1H, m), 4.47 (1H, s), 6.87 (1H, dd), 7.08 (1H, d), 7.26 (2H, d), 7.36 (1H, d), 7.44 (2H, d)

18	4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-4-hydroxy-α-(2-methoxyphenyl)-1-piperidineacetic acid	523/525	δ (CD_3OD) 1.65 - 1.80 (4H, m), 1.93 - 2.04 (4H, m), 2.40 (2H, s), 2.48 - 2.57 (2H, m), 2.81 - 2.89 (2H, m), 2.94 - 3.06 (2H, m), 3.67 - 3.77 (2H, m), 3.91 (3H, s), 4.32 - 4.39 (1H, m), 4.98 (1H, s), 6.87 (1H, dd), 7.03 (1H, td), 7.08 (1H, d), 7.09 - 7.12 (1H, m), 7.36 (1H, d), 7.41 - 7.46 (1H, m), 7.53 (1H, dd)
23	methyl 4-[[4-(2,4-dichloro-3-methylphenoxy)-1-piperidinyl]methyl]-1-piperidineacetate	429/431	
24	methyl 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-4-hydroxy-1-piperidineacetate	431/433	
26	Methyl (2*S*)-2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)propanoate	429/431	
28	4-[[4-(2,4-dichloro-3-methylphenoxy)-1-piperidinyl]methyl]-1-piperidineacetic acid	415/417	δ ($CDCl_3$) 1.45 - 1.61 (2H, m), 1.80 - 1.93 (3H, m), 1.96 - 2.10 (4H, m), 2.33 (2H, d), 2.38 - 2.48 (2H, m), 2.47 (3H, s), 2.71 - 2.82 (2H, m), 3.01 (2H, t), 3.55 - 3.68 (2H, m), 3.59 (2H, s), 4.44 - 4.54 (1H, m), 6.96 (1H, d), 7.27 (1H, d)

29	4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-4-hydroxy-1-piperidineacetic acid	417/419	
30	(2*R*)-2-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)propanoic acid	415/417	δ (CD_3OD) 1.42 - 1.59 (5H, m), 1.71 - 2.12 (7H, m), 2.28 - 2.41 (4H, m), 2.70 - 2.80 (2H, m), 2.93 - 3.14 (2H, m), 3.49 - 3.62 (3H, m), 4.37 - 4.46 (1H, m), 6.91 (1H, dd), 7.12 (1H, d), 7.40 (1H, t)
31	(2*S*)-2-(4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)propanoic acid	415/417	δ (CD_3OD) 1.44 - 1.60 (5H, m), 1.73 - 2.12 (7H, m), 2.30 - 2.43 (4H, m), 2.71 - 2.81 (2H, m), 2.93 - 3.14 (2H, m), 3.50 - 3.62 (3H, m), 4.38 - 4.48 (1H, m), 6.91 (1H, dd), 7.12 (1H, d), 7.40 (1H, d)
36	2-[(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)methyl]benzoic acid	477/479	δ (CD_3OD) 1.30 - 1.46 (2H, m), 1.70 - 1.83 (3H, m), 1.95 - 2.11 (4H, m), 2.25 - 2.41 (4H, m), 2.69 - 2.79 (2H, m), 2.94 (2H, t), 3.31 - 3.41 (2H, m), 4.26 (2H, s), 4.41 (1H, dt), 6.90 (1H, dd), 7.11 (1H, d), 7.39 (2H, d), 7.51 (2H, dtd), 7.97 (1H, dd)

EXAMPLE 37

Pharmacological Analysis: Calcium flux $[Ca^{2+}]_i$ assay

Human eosinophils

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended ($5x10^6$ ml^{-1}) and loaded with 5μM FLUO-3/AM + Pluronic F127 2.2μl/ml (Molecular Probes) in low potassium solution (LKS; NaCl 118mM, $MgSO_4$ 0.8mM, glucose 5.5mM, Na_2CO_3 8.5mM, KCl 5mM, HEPES 20mM, $CaCl_2$ 1.8mM, BSA 0.1%, pH 7.4) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at $2.5x10^6$ ml^{-1}. The cells were then transferred to 96 well FLIPr plates (Poly-D-Lysine plates from Becton Dickinson pre-incubated with 5μM fibronectin for two hours) at 25μl/well. The plate was centrifuged at 200g for 5min and the cells were washed twice with LKS (200μl; room temperature).

A compound of the Examples was pre-dissolved in DMSO and added to a final concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an A_{50} concentration of eotaxin and the transient increase in fluo-3 fluorescence (l_{Ex} =490nm and l_{Em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

Compounds of the Examples were found to be antagonists if the increase in fluorescence induced by eotaxin (a selective CCR3 agonist) was inhibited in a concentration dependent manner. The concentration of antagonist required to inhibit the fluorescence by 50% can be used to determine the IC_{50} for the antagonist at the CCR3 receptor.

EXAMPLE 38

Human eosinophil chemotaxis

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended at $10x10^6$ ml^{-1} in RPMI containing 200 IU/ml penicillin, 200 μg/ml streptomycin sulfate and supplemented with 10% HIFCS, at room temperature.

Eosinophils (700 μl) were pre-incubated for 15 mins at 37° C with 7 μl of either vehicle or compound (100x required final concentration in 10% DMSO). The chemotaxis

plate (ChemoTx, 3μm pore, Neuroprobe) was loaded by adding 28μl of a concentration of eotaxin 0.1 to 100nM (a selective CCR3 agonist over this concentration range) containing a concentration of a compound according to the Examples or solvent to the lower wells of the chemotaxis plate. The filter was then placed over the wells and 25 μl of eosinophil suspension were added to the top of the filter. The plate was incubated for 1 hr at 37° C in a humidified incubator with a 95% air/5% CO_2 atmosphere to allow chemotaxis.

The medium, containing cells that had not migrated, was carefully aspirated from above the filter and discarded. The filter was washed once with phosphate buffered saline (PBS) containing 5 mM EDTA to remove any adherent cells. Cells that had migrated through the filter were pelleted by centrifugation (300xg for 5 mins at room temperature) and the filter removed and the supernatant transferred to each well of a 96-well plate (Costar). The pelleted cells were lysed by the addition of 28 μl of PBS containing 0.5% Triton x100 followed by two cycles of freeze/thawing. The cell lysate was then added to the supernatant. The number of eosinophils migrating was quantified according to the method of Strath et al., *J. Immunol. Methods*, 1985, 83, 209 by measuring eosinophil peroxidase activity in the supernatant.

Compounds of the Examples were found to be antagonists of eotaxin mediated human eosinophil chemotaxis if the concentration response to eotaxin was shifted to the right of the control curve. Measuring the concentration of eotaxin required to give 50% chemotaxis in the presence or absence of compounds enables the apparent affinity of the compounds at CCR3 to be calculated.

Example	% inhibition at 1μM
1	96
4	90
10	108
13	87

EXAMPLE 39

Guinea-pig isolated trachea

(See for example, Harrison, R.W.S., Carswell, H. & Young, J.M. (1984) European J. Pharmacol., 106, 405-409.)

Male albino Dunkin-Hartley guinea-pigs (250g) were killed by cervical dislocation and the whole trachea removed. After clearing the adherent connective tissue, the trachea was cut into six ring segments each three cartilage bands wide and then suspended in 20ml organ baths containing Krebs-Henseleit solution of the following composition (mM): NaCl 117.6, NaH_2PO_4 0.9, $NaHCO_3$ 25.0, $MgSO_4$ 1.2, KCl 5.4, $CaCl_2$ 2.6 and glucose 11.1. The buffer was maintained at 37°C and gassed with 5% CO_2 in oxygen. Indomethacin (2.8μM) was added to the Krebs solution to prevent development of smooth muscle tone due to the synthesis of cyclo-oxygenase products. The tracheal rings were suspended between two parallel tungsten wire hooks, one attached to an Ormed beam isometric force transducer and the other to a stationary support in the organ bath. Changes in isometric force were recorded on 2-channel Sekonic flat bed chart recorders.

Experimental protocols

At the beginning of each experiment a force of 1g was applied to the tissues and this wa reinstated over a 60 minute equilibration period until a steady resting tone was achieved. Subsequently, a cumulative histamine concentration effect (E/[A]) curve was constructed at 0.5 log_{10} unit increments, in each tissue. The tissues were then washed and approximately 30 minutes later, test compound or vehicle (20% DMSO) was added. Following an incubation period of 60 minutes a second E/[A] curve was performed to histamine.

Contraction responses were recorded as a percentage of the first curve maximum.

Data analysis

Experimental E/[A] curve data were analysed for the purposes of estimating the potencies ($p[A_{50}]$ values) of histamine in the absence and presence of the test compound. Affinity (pA_2) values of test compounds were subsequently calculated using the following equation:

$$\log(r-1) = \log[B] + pA_2$$

where $r = [A]_{50}$ in presence of test compound/$[A]_{50}$ in absence of antagonist and [B] is the concentration of test compound. Compounds of the Examples were found to be H1 antagonists.

EXAMPLE 40

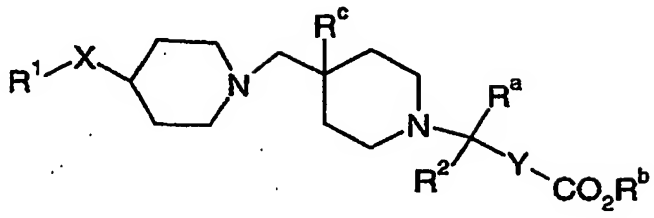
Histamine H1 receptor binding activity of compounds of the invention was assessed by competition displacement of 1nM [3H]-pyrilamine (Amersham, Bucks, Product code TRK 608, specific activity 30Ci/mmol) to 2μg membranes prepared from recombinant CHO-K1 cells expressing the human H1 receptor (Euroscreen SA, Brussels,

Belgium, product code ES-390-M) in assay buffer (50mM Tris pH 7.4 containing 2mM $MgCl_2$, 250mM sucrose and 100mM NaCl) for 1 hour at room temperature.

Example	H1 pKi /[1328_S]
1	7.2
2	7.5
3	7.4
4	7.0
5	7.1
6	7.7
7	7.1
8	7.3
9	7.5
10	6.6
11	6.8
12	6.7
13	7.6
14	7.6
15	7.6
17	8.0
18	7.8
19	8.1
24	6.9
27	6.9
28	6.7
29	7.0
32	6.7
35	8.0

CLAIMS

1. A compound of formula (I):



(I)

wherein:

X is CH_2, C(O), O, S, S(O), $S(O)_2$ or NR^3;

Y is a bond, C_{1-6} alkylene (optionally substituted by C_{1-4} alkyl or phenyl) or phenylene (optionally substituted by halogen, hydroxy, C_{1-4} alkyl or C_{1-4} alkoxy);

R^a and R^b are, independently, hydrogen or C_{1-4} alkyl;

R^c is hydrogen or hydroxy;

R^1 is hydrogen, C_{1-6} alkyl, aryl or heterocyclyl;

R^2 is hydrogen, C_{1-4} alkyl, aryl or heterocyclyl;

wherein, unless stated otherwise, the foregoing aryl and heterocyclyl moieties are optionally substituted by: halogen, cyano, nitro, hydroxy, oxo, $S(O)_pR^4$, $OC(O)NR^5R^6$, NR^7R^8, $NR^9C(O)R^{10}$, $NR^{11}C(O)NR^{12}R^{13}$, $S(O)_2NR^{14}R^{15}$, $NR^{16}S(O)_2R^{17}$, $C(O)NR^{18}R^{19}$, $C(O)R^{20}$, CO_2R^{21}, $NR^{22}CO_2R^{23}$, C_{1-6} alkyl, CF_3, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkoxy, OCF_3, C_{1-6} alkoxy(C_{1-6})alkoxy, C_{1-6} alkylthio, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl (itself optionally substituted by C_{1-4} alkyl or oxo), methylenedioxy, difluoromethylenedioxy, phenyl, phenyl(C_{1-4})alkyl, phenoxy, phenylthio, phenyl(C_{1-4})alkoxy, heterocyclyl, heterocyclyl(C_{1-4})alkyl, heterocyclyloxy or heterocyclyl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heterocyclyl moieties are optionally substituted with halogen, hydroxy, nitro, $S(O)_q$(C_{1-4} alkyl), $S(O)_2NH_2$, $S(O)_2NH$(C_{1-4} alkyl), $S(O)_2N$(C_{1-4} alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 below), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, C(O)NH(C_{1-4} alkyl), C(O)N(C_{1-4} alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 below), CO_2H, CO_2(C_{1-4} alkyl), NHC(O)(C_{1-4} alkyl), $NHS(O)_2$(C_{1-4} alkyl), C(O)(C_{1-4} alkyl), CF_3 or OCF_3;

p and q are, independently, 0, 1 or 2;

R^3, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-6}$ alkenyl), phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 below),cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 below), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 below), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 below), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3);

alternatively NR^5R^6, NR^7R^8, $NR^{12}R^{13}$, $NR^{14}R^{15}$, $NR^{18}R^{19}$, may, independently, form a 4-7 membered heterocyclic ring, azetidine, pyrrolidine, piperidine, azepine, morpholine or piperazine, the latter optionally substituted by C_{1-4} alkyl on the distal nitrogen;

R^4, R^{17} and R^{23} are, independently, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-6}$ alkenyl), phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl),

$S(O)_2N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3);

or an N-oxide thereof; or a pharmaceutically acceptable salt thereof; or a solvate thereof.

2. A process for preparing a compound of formula (I) as claimed in claim 1.

3. A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, and a pharmaceutically acceptable adjuvant, diluent or carrier.

4. A compound of the formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, for use in therapy.

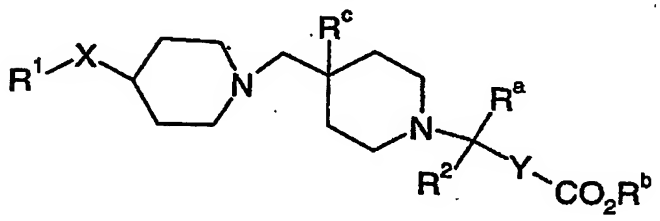
5. A compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, in the manufacture of a medicament for use in therapy.

6. A method of treating a chemokine mediated disease state in a mammal suffering from, or at risk of, said disease, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1.

ABSTRACT

CHEMICAL COMPOUNDS

The present invention provides a compound of a formula (I):



(I)

wherein the variables are defined herein; to a process for preparing such a compound; and to the use of such a compound in the treatment of a chemokine (such as CCR3) or H1 mediated disease state.